

## REMARKS

Opioid drugs, such as morphine, are among the most powerful and widely used analgesics known. These drugs, however, are not without untoward side effects, most notably of which are the sedative and addictive effects of these drugs on the central nervous system (CNS). The present invention provides new opioid drugs that, while retaining activity in the peripheral nervous system, do not affect the CNS, due to the fact that these drugs cannot gain access to the CNS. Central to this advantage of these new drugs is the linkage of a charged group, via a spacer, to position N17 of the basic opioid structure. The charged group, which, by increasing the hydrophilicity of the drug, prevents passage of the drug across the blood-brain barrier into the CNS, has no adverse effects on drug efficiency.

### Summary of the Office Action

Examination of claims 1-27 is reported in the present Office Action. Claims 5, 6, 11-14, 17, and 19-27 were objected to under 37 C.F.R. § 1.75(c); claims 1-14 and 17-27 were rejected under 35 U.S.C. § 112, first paragraph; claims 1-27 were rejected under 35 U.S.C. § 112, second paragraph; claims 1-7, 17-18, and 23-27 were rejected under 35 U.S.C. § 102(b); and claims 1-7 and 15-27 were rejected under 35 U.S.C. § 103(a). The objection and rejections are addressed as follows. First, applicants note that, as required by the Examiner, an abstract has been added to the application.

Objection under 37 C.F.R. § 1.75(c)

Claims 5, 6, 11-14, 17, and 19-27 were objected to under 37 C.F.R. § 1.75(c) as being in improper form, because a multiple dependent claim may not be dependent upon another multiple dependent claim. Applicants have overcome this rejection by amending these claims to be in proper dependent form.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-14 and 17-27 were rejected under § 112, first paragraph, with the Examiner stating that the specification does not provide sufficient enablement of the range of compounds defined in the claims. This rejection should be withdrawn.

Once in possession of applicants' inventive concept, the recognition that a spacer and charged group at position 17 reduce the lipophilicity of morphine-related opioid compounds, and thereby restrict their access to the CNS, a person skilled in the art would have had sufficient information to be able to carry out the invention across the scope of the claims. The examples provided in the specification demonstrate this principle using different spacers and two different highly charged groups. Utilizing this information would have been a matter of routine experimentation, well within the capacity of a person skilled in the art, and particularly so in the light of the availability of modern methods of combinatorial synthesis and automated screening, to determine whether a given compound falls within the scope of the claims.

The starting materials, such as the compounds set out in Table 1, were all known; either their syntheses were known, or the compounds themselves were commercially

available. For example, the 1994 Sigma catalogue lists many of the opioids of Table I as being for sale at this time (copies of the relevant pages are enclosed). The following is a list of commercially available opioids from the Sigma (1994) catalogue, with the catalogue number provided in parentheses: Oxymorphone (O1503), morphine (M8777), codeine (C5901), ethylmorphine (E8512), hydrocodone (H4516), hydromorphone (H5136), oxycodone (O1378), thebaine (T2019), buprenorphine (B9275), levorphanol(P6527), and pentazocine (P6527). These and other known starting materials could have been employed in the general procedures that are described in Examples 1 through 4 of the application, to obtain compounds that are within applicants' claims. The skilled person would have had no difficulty in obtaining the starting compounds, or in synthesizing them using known techniques. This rejection should therefore be withdrawn.

#### Rejections under 35 U.S.C. § 112, second paragraph

Claims 1 and 7 were rejected under § 112, second paragraph, with the Examiner stating that the term "general" is unclear. The term "general" has been deleted from these claims.

Claims 1, 7, and 18 were rejected under § 112, second paragraph as being indefinite in the use of the term "opioid compound." This rejection should be withdrawn.

As is noted above, claims 1, 7, and 18 have been amended to specify that the compounds of these claims include "an opioid that is structurally related to morphine," consistent with the definition of the term "opioid" at page 3, lines

29-31 of the specification. Applicants respectfully submit that one of skill in this art would understand what compounds are included within the scope of this claim, as it is well understood in the art what is meant by “structurally related to morphine.” For example, a detailed discussion of the structure of morphine and related opioids is provided in the enclosed excerpt from Gilman and Goodman, “The Pharmacological Basis of Therapeutics,” 7<sup>th</sup> edition, which is an authoritative reference book in this field. On page 496 of this excerpt, it is noted that common characteristics of morphine and related opioids are indicated by the heavy lines in the drawing on page 495, and these heavy lines outline a three ring structure, including a nitrogen at position 17 within a piperidine ring. Thus, one of skill in this art would understand that a compound that is “structurally related to morphine” would include these three rings, as well as a nitrogen at position 17 of the piperidine ring.

Claims 1, 7, and 18 were also rejected under § 112, second paragraph, as lacking antecedent basis for the term “nitrogen at position 17.” This rejection can now be withdrawn, as these claims have been amended to specify that “N is a nitrogen atom that corresponds to position 17 of morphine,” and thus no longer refer to an atom that is not specified in formula I.

Claims 2-4 were rejected under § 112, second paragraph, on the basis that the substituents on the various groups are not defined. This rejection should be withdrawn.

It is well understood in the art that groups such as alkyl, alkenyl, or alkynyl, as are specified in claims 2 and 3, can have hydrogen atoms of these groups substituted with other atoms or groups. Any such substitutions would be acceptable and within these

claims, provided that the overall resultant compound has activity at opiate receptors and the charged group of the compound functions to restrict access of the compound to the CNS. Thus, for example, such substituents could include halides (Br, Cl, F, or I), fully or partially halogenated alkyl groups (such as CF<sub>3</sub>), NH<sub>2</sub>, hydroxy, alkoxy groups (such as methoxy), substituted amino groups, and carboxyl groups. This rejection should therefore be withdrawn.

Claim 7 was rejected under § 112, second paragraph, with the Examiner questioning the meaning of “H<sub>1</sub>” within the definition of “R<sub>1</sub>.” The term “H<sub>1</sub>” does not appear in this claim. Rather, the term “H,” meaning hydrogen, is included in this claim in the definition of R<sub>1</sub>. This rejection should therefore be withdrawn.

Claim 7 was also rejected under § 112, second paragraph, with the Examiner stating that the definition of “YN-” in formula II is confusing in relation to formula IIIb. In the interest of expediting prosecution, applicants have overcome this rejection by deleting references to compounds of formula IIIb from claim 7. Applicants reserve the right to pursue the original or similar claims in further applications.

Claim 18 was rejected under § 112, second paragraph, as being unclear in the use of the word “optionally.” This rejection should be withdrawn, as the word “optionally” does not appear in claim 18.

Claims 26 and 27 were rejected under §§ 112, second paragraph and 101 for claiming a use without setting forth any steps involved in the process involved in this use. These claims have been canceled.

### Rejections under 35 U.S.C. § 102(b)

Claims 1-5, 7, 18, and 23-25 were rejected under § 102(b) as being anticipated by Albertson et al. (U.S. Patent No. 4,108,857); Atsumi et al. (U.S. Patent No. 3,950,346); Yokoyama et al. (J. Med. Chem. 22(5):537-553, 1979); Atsumi et al. (JP Patent No. 49-072261-A2); Uwaydah et al. (J. Med. Chem. 22(7):889-890, 1979); and Maeda et al. (Pharmacobio-Dyn. 4(3):167-174, 1981). These rejections should be withdrawn.

Claim 1, as well as claims 2-5, 7, 18, and 23-25, which depend from claim 1, each require an opioid compound that is structurally related to morphine, and is linked via a spacer to a charged group. In none of the compounds of the cited references is an opioid linked to a charged group. Rather, in each of the compounds of Atsumi, Yokoyama, Uwaydah, and Maeda, an amide group, which, as is well known in the art, is uncharged, is linked to an opioid. These rejections should therefore be withdrawn.

Claims 1-4 were rejected under § 102(b) as being anticipated by Hogan (WO Patent No 94-01102-A1). This rejection should be withdrawn.

First, applicants note that, in the compound of Hogan that is cited in this rejection, there is no net charge on the substituent attached to the nitrogen in position 17. In particular, while the hydrazine linkage of Hogan contains both formal positive and negative charges, the net charge on the linker/substituent is zero. Thus, as no net charge is added to the codeine by attachment of the probe at nitrogen 17, Hogan does not teach all of the elements of the rejected claims, which require a charged group at this position. This rejection should therefore be withdrawn.

Applicants also note that, as is discussed above, the compounds of the present claims each include a charged group on a spacer that is attached to nitrogen 17 of an opioid, and that this charged group, as described within the specification, must be one that prevents access of the compound to the CNS. In Hogan, no mention is made as to whether the compounds disclosed are similarly restricted. Indeed, the compounds of Hogan include an aminimide group in the position corresponding to the charged group of the compounds of the present claims. As is noted by Hogan (see, e.g., pages 33 and 73-78, as well as claim 41), aminimide groups are lipophilic. Thus, in contrast to the charged groups of the compounds of the present claims, which restrict access to the CNS, the aminimide groups of the compounds of Hogan are likely to facilitate CNS access. Moreover, there is no indication that the compounds of Hogan are active at opiate receptors, as is required of the compounds of the present claims. This rejection should therefore be withdrawn.

The Examiner rejected claims 1-7, 17-18, and 23-27 under § 102(b) as being anticipated by Jackson et al. (Clin. Exp. Pharmacol. Physiol. 19(1):17-23, 1992). Specifically, the Examiner cites compound (23) on page 22. The compounds of the rejected claims are required to have activity at opiate receptors. In contrast, compound 23 of Jackson does not have such activity. For example, at page 23, line 8, Jackson states that “[p]reliminary testing, in isolated guinea-pig ileum showed no  $\mu$ -receptor opioid activity.” Because, as is noted above, the compounds of the present claims must have activity at the opiate receptors, this rejection should be withdrawn.

### Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-7 and 15-27 under § 103(a) for obviousness over Jackson, in view of Green et al. ("Protective Groups in Organic Synthesis," 2<sup>nd</sup> Edition, John Wiley and Sons, Inc, New York, pages 12 and 77) or Scheinmann (U.S. Patent No. 5,977,326). This rejection should be withdrawn.

The Examiner states that Jackson teaches that the introduction of a polar alkyl guanidine onto the nitrogen atom of morphine would result in a molecule that retains its analgesic effect, while eliminating its CNS effect. However, as is noted above, the compound of Jackson that is specifically named by the Examiner, compound 23, is inactive at opiate receptors (see, e.g., pages 22 and 23 of the reference, as well as page 2, lines 31-37 of the present specification). Thus, the Jackson reference, in teaching the inactivity of morphine derivatives having N17 substitutions, teaches away from the possibility of obtaining active molecules by making such substitutions. Motivation to use this approach to make active opioid compounds is thus not provided by Jackson, nor, as is discussed further below, by either of the other references cited in this rejection.

The Examiner states that compound 23 of Jackson differs from compound KRS41 of the present invention (claim 16) in having t-butyl-dimethyl-silyl at position 3, instead of hydroxy. The Examiner further notes that Green teaches that t-butyl-dimethyl-silyl is a well known protecting group for hydroxy, and that Scheinmann teaches that silyl and hydrogen are optional substituents on morphine. Thus, the Examiner concludes that it would have been obvious to remove the silyl protecting group to obtain the active hydroxy morphine compound of the present invention. The Examiner also concludes that



one of skill in the art would have been motivated to substitute Jackson's silyl with hydrogen, to arrive at the instant invention. Applicants respectfully disagree.

As is noted above, the compound of Jackson is inactive, and thus those of skill in the art would not have been motivated to use the approach of Jackson to make compounds that are active at opiate receptors. There was no reason to have believed that removing the protecting group would have yielded an active molecule, prior to the present invention. Indeed, in looking for active molecules, it would appear that Jackson would have been motivated to remove the protecting groups, if it were obvious to do so. Jackson did not remove these groups, and even went through the trouble of testing the protected compound. Thus, clearly it would not have been obvious to obtain active compounds by this approach. The teachings of Green and/Scheinmann do not overcome this teaching away. Green is a general reference that teaches t-butyl-dimethyl silyl protecting groups, but nowhere does Green mention whether the presence of these groups would impact the activity or CNS accessibility of an N17 modified morphine-like opioid, like those of the present claims. Scheinmann describes morphine-based molecules that can include silyl and hydrogen as optional substituents, but Scheinmann provides no indication of how the presence of such substituents could impact the activity or CNS-accessibility of a morphine-based molecule having a charged group at N17.

Thus, because Jackson teaches away from the present invention, and because neither of the other cited references, Green and Schienmann, would have provided any motivation to modify the compounds of Jackson to obtain those of the present invention, this rejection should be withdrawn.

### Support for the Amendments to the Specification

Amendments have been made to the specification to correct a number of clerical errors. These include errors on page 3, line 37 (replacing “alkenyl,” second instance, with “alkynyl”), page 11, line 11 (insert “a” before “third”), page 14, line 26 (replace “chemical” with “clinical”), page 33, line 10 (replace “KRS-3-36” with “KRS-3-56”), and page 12, line 17 (including a missing arrow in a reaction).

Page 12, line 2 was amended to include “Pyrazole.” Support for this amendment can be found, for example, at page 24, lines 24 and 25; page 28, lines 15 and 16; and page 29, line 25.

Page 10, line 17 was amended to include structural details for metazocine in the third table. Metazocine is mentioned at page 6, line 11. The structure of this compound is well known, as is indicated in the attached extract from the Merck Index (11<sup>th</sup> edition, 1989), and consequently it is submitted that this amendment does not introduce new matter.

Page 13, line 21 was amended to include  $\text{CH}_3\text{AlClNR}^1\text{R}^2$  (methylchloroaluminum amide) to the formula. Support for this amendment may be found, for example, in Examples 9, 13, 15-18, and 20. See for example, page 26, line 19.

### CONCLUSION

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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The marked-up specification

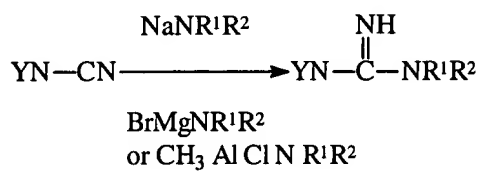
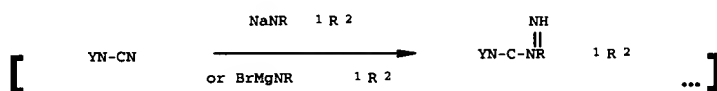
Table on page 10, lines 17-20.

R	X	Name
CH <sub>3</sub>	H	Eptazocine
Me <sub>2</sub> C=CHCH <sub>2</sub> -	CH <sub>3</sub>	Pentazocine
<u>CH<sub>3</sub></u>	<u>CH<sub>3</sub></u>	<u>Metazocine</u>

Page 12, lines 2-3 with the following.

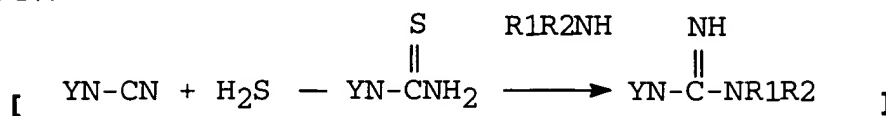
wherein L is a suitable leaving group, for example CH<sub>3</sub>O, CH<sub>3</sub>S, CH<sub>3</sub>SO<sub>2</sub>, SO<sub>3</sub>H, pyrazole or

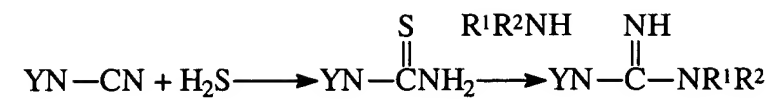
Page 13, line 15.



ex 13

Page 12, line 17.





Paragraph on page 11, lines 11-17.

According to a third aspect, the invention provides a method of reducing the central nervous system activity of an opioid compound, comprising the step of linking the nitrogen atom at position 17 of said compound to a spacer group, which in turn is linked to a charged group. Optionally the linkage to the charged group is via a spacer group.

Paragraph on page 14, lines 22-26.

The dosage to be used will depend on the nature and severity of the condition to be treated, and will be at the discretion of the attending physician or veterinarian. The most suitable dosage for a specific condition can be determined using normal [chemical] clinical trial procedures.

Paragraph on page 3, line 34.

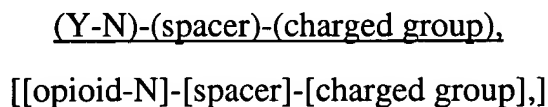
The spacer can be any spacer group of dimensions approximately equivalent to an alkyl chain of 1 to 6 carbon atoms, and may for example be a straight or branched alkyl, alkenyl or [alkenyl] alkynyl chain of 1 to 6 carbon atoms, which may optionally be substituted. The spacer also comprises a cyclic alkyl, alkenyl, or alkynyl group. Preferably the spacer group is unsubstituted, and more preferably is of 2 to 3 carbons atoms. The charged group may be any group which has the ability to restrict access of the compound of formula I to the central nervous system, and is preferably an amidine or guanidine group.

Paragraph on page 33, lines 10-14.

The effects of compounds [KRS-3-36] KRS-3-56 and KRS-41 on the central nervous system were compared with that of morphine using a standard Irwin test (Irwin, S.; Psychopharmacologic (Berlin), 1968 13 222-257). The relevant results are shown in Tables 4 and 5.

The marked-up claims

1. (Amended) A [An opioid] compound of [general] formula I:



I

where said [opioid] compound has activity at opiate receptors [in which an “opioid” compound is linked via the nitrogen at position 17 to a spacer group, which in turn is linked to a charged group,] and wherein Y is an opioid that is structurally related to morphine, N is a nitrogen atom that corresponds to position 17 of morphine, to which is linked a spacer, which links said compound to a charged group or a pharmaceutically acceptable salt thereof [,where said opioid compound has activity at opiate receptors].

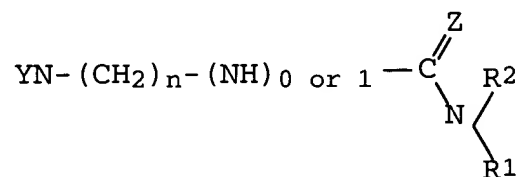
2. (Amended) A compound according to Claim 1, in which the spacer is a straight or branched alkyl, alkenyl or [alkenyl] alkynyl chain of 1 to 6 carbon atoms, which may optionally be substituted.

4. (Amended) A compound according to [any one of Claims 1 to 3]Claim 1, in which the spacer group is unsubstituted.

5. (Amended) A compound according to [any one of Claims 1 to 4]Claim 1, in which the spacer group is of 2 to 3 carbon atoms.

6. (Amended) A compound according [to any one of Claims 1 to 5]Claim 1, in which the charged group is an amidine or guanidine group.

7. (Amended) A compound according to Claim 1, of [general] formula (II)



in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of [compound of general] formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR<sup>3</sup>;

R<sup>1</sup> is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R<sup>2</sup> is H or an alkyl group having 1 to 6 carbon atoms;

R<sup>3</sup> is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

$R^1$  and  $R^3$  may together complete an addition ring,  
or a pharmaceutically acceptable salt thereof.

11. (Amended) A compound according to [any one of Claims 8 to 10]Claim 8, in which n is 2 or 3.

12. (Amended) A compound according to [any one of Claims 8 to 11]Claim 8, in which Z is NH, and  $R^1$  and  $R^2$  are both H.

13. (Amended) A compound according to [any one of Claims 8 to 11]Claim 8, in which the opioid structurally related to morphine [precursor of YN- or  $Y^1NR^4$ -] is a compound selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxycodone, dihydrocodeine, thebaine, metopon, etorphine, acetorphine, [ketobemidone, ethoheptazine,] diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine and metazocine.

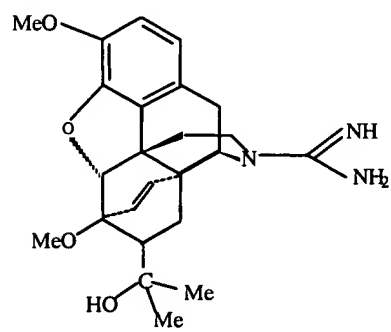
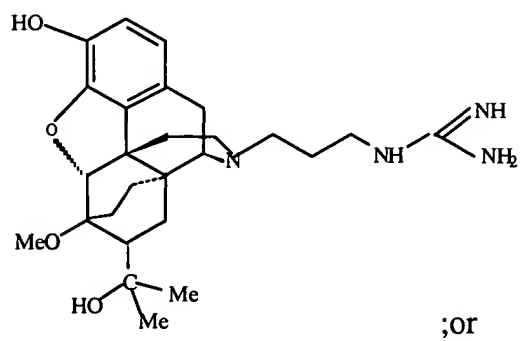
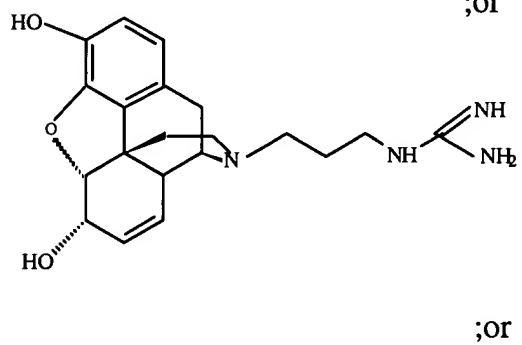
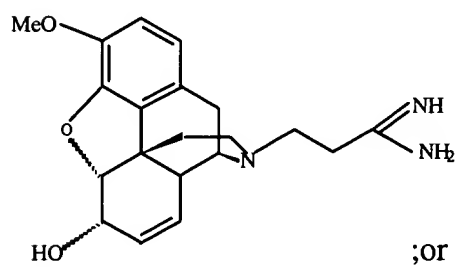
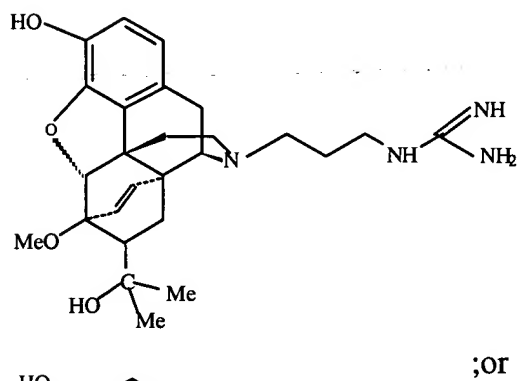
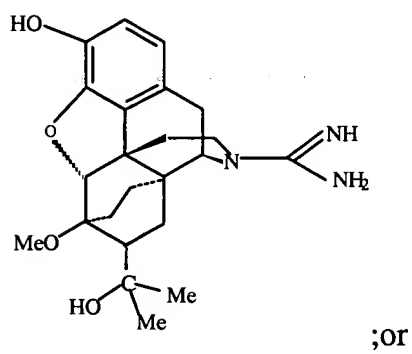
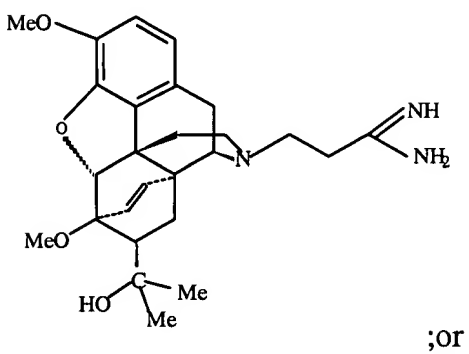
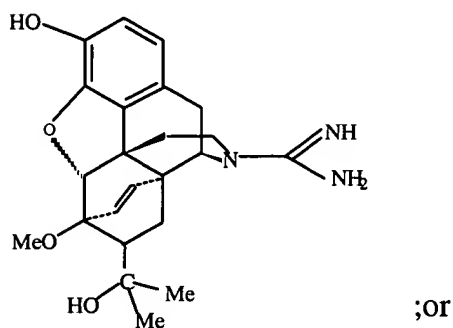
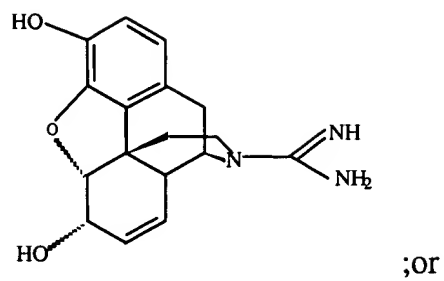
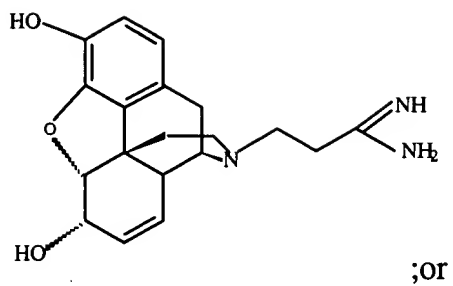
14. (Amended) A compound according to Claim 12, in which the opioid structurally related to morphine [precursor of YN- or  $Y^1NR^4$ -] is morphine, codeine or buprenorphine.

15. (Amended) A compound according to Claim 1, in which the opioid structurally related to morphine [compound of formula (IIIa)] is selected from the group [set out in Table 1] consisting of morphine, codeine, ethylmorphine, heroin, O-carboxymethylmorphine, O-acetylmorphine, disilyl morphine, disilyl normorphine, etorphine, acetorphine, diprenorphine, buprenorphine, hydrocodone, hydromorphone,

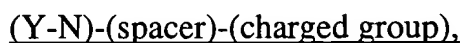


oxymorphone, oxycodone, metopon, phenomorphan, levorphanol, dihydrocodeine, thebaine, hydrocodeine, pentazocine, eptazocine and metazocine.

16. (Amended) A compound according to Claim 1, in which the [opioid] compound of formula I is selected from the group consisting of [KRS-41, KRS-2-19, KRS-3-7, KRS-3-23-4, KRS-3-28, KRS-3-30-2, KRS-3-56, KRS-2-63, KRS-4-8, and KRS-2-47, as herein defined.]

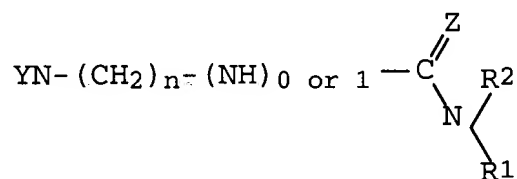


17. (Amended) An opiate receptor agonist having analgesic properties and having reduced or no CNS activity, of [general] formula I; [or general formula II as defined in any one of claims 1 to 15.]



(I)

Where said compound has activity at opiate receptors and wherein Y is an opioid that is structurally related to morphine, N is a nitrogen atom that corresponds to position 17 of morphine, to which is linked a spacer, which links said compound to a charged group or a pharmaceutically acceptable salt thereof, or general formula II:



(II)

in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)



(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR<sup>3</sup>;

R<sup>1</sup> is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R<sup>2</sup> is H or an alkyl group having 1 to 6 carbon atoms;

R<sup>3</sup> is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

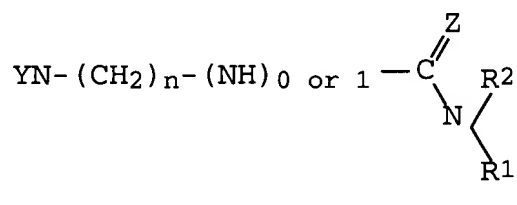
n is an integer of 1 to 6,

and wherein

R<sup>1</sup> and R<sup>3</sup> may together complete an addition ring.

18. (Amended) A method of reducing the central nervous system activity of an opioid structurally related to morphine [compound], comprising the step of linking the nitrogen atom at position 17 of said opioid structurally related to morphine [compound] to a spacer group, which in turn is linked to a charged group.

19. (Amended) A method for the preparation of a compound of formula II [as defined in any one of Claims 8 to 13,]



in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR<sup>3</sup>;

R<sup>1</sup> is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R<sup>2</sup> is H or an alkyl group having 1 to 6 carbon atoms;

R<sup>3</sup> is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

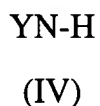
n is an integer of 1 to 6,

and wherein

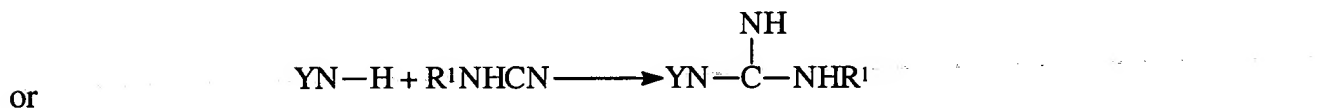
R<sup>1</sup> and R<sup>3</sup> may together complete an addition ring,

[in which YN- may be replaced by Y<sup>1</sup>NR<sup>4</sup>-, ]comprising the steps of

(a) Reaction of a compound of formula (IV)

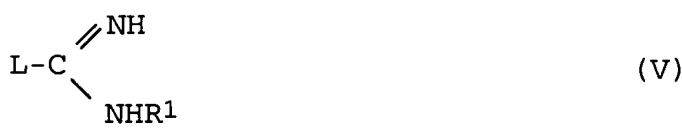


with a cyanamide, R<sup>1</sup>NHCN, according to the equation

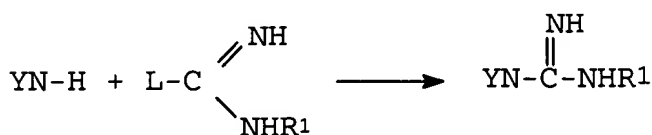


(b) Reaction of a compound of formula (IV) with a compound of formula

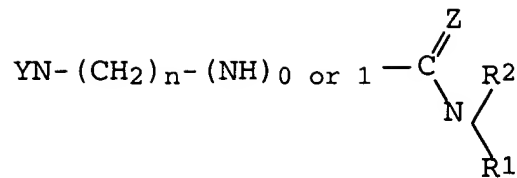
(V)



wherein L is a leaving group, according to the equation



20. (Amended) A method for the preparation of a compound of formula II [as defined in any one of Claims 8 to 13]



in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR<sup>3</sup>;

R<sup>1</sup> is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R<sup>2</sup> is H or an alkyl group having 1 to 6 carbon atoms;

R<sup>3</sup> is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

R<sup>1</sup> and R<sup>3</sup> may together complete an addition ring,

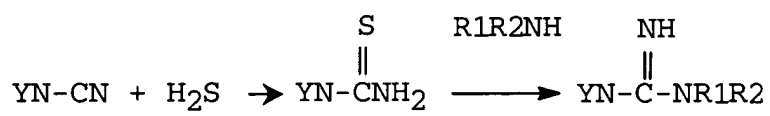
[in which Z is NR<sup>3</sup>, ]comprising the steps of

(a) Reaction of a compound of [the] formula (VI)



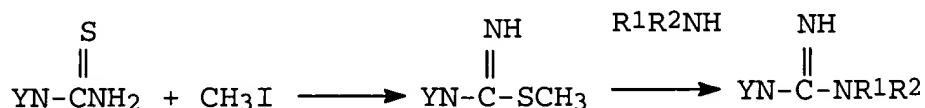
(VI)

with  $\text{H}_2\text{S}$  to obtain an N-thiocarboxamide  $\text{YN-CSNH}_2$ , and optionally reacting the  $\text{YN-CSNH}_2$  [which is reacted] with an amine  $\text{R}^1\text{R}^2\text{NH}$  according to the first stage or optionally the two stages of the [two-stage] equation

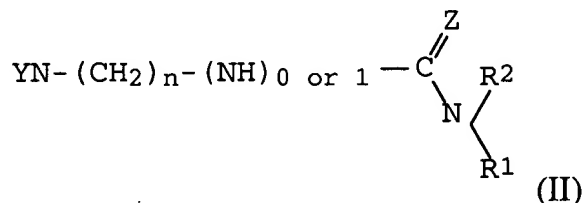


to yield a compound of formula II [compounds of the invention] where Z is S if the optional step is not taken, or a compound of formula II [and] where Z is NH if the optional step is taken, or

(b) Methylating the N-thiocarboxamide to yield an isothiurea compound, which is in turn reacted with an amine  $\text{R}^1\text{R}^2\text{NH}$ :



21. (Amended) A method of synthesis of a compounds of formula (II) [as defined in any one of Claims 8 to 13,]



in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR<sup>3</sup>;

R<sup>1</sup> is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R<sup>2</sup> is H or an alkyl group having 1 to 6 carbon atoms;

R<sup>3</sup> is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

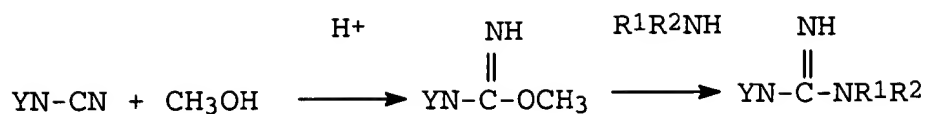
R<sup>1</sup> and R<sup>3</sup> may together complete an addition ring,

comprising the step of reacting an N-cyano compound of formula (VI) [as defined in Claim 19]

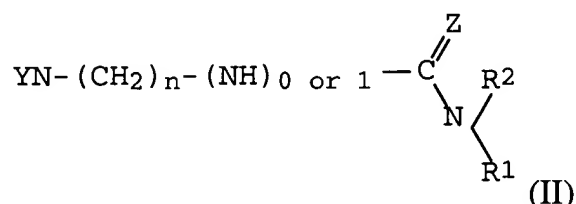
YN-CN

with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine according to the equation





22. (Amended) A method of synthesis of a compound of formula (II) [as defined in any one of Claims 8 to 13]



in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)



(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is NH;

R<sup>1</sup> is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R<sup>2</sup> is H or an alkyl group having 1 to 6 carbon atoms;

n is an integer of 1 to 6,

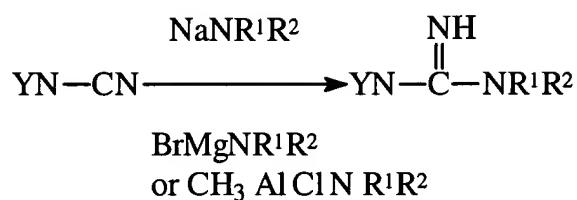
and wherein

R<sup>1</sup> and R<sup>3</sup> may together complete an addition ring,

[in which Z is N, ]comprising the step of reacting an N-cyano compound of formula (VI)  
[as defined in Claim 19]



and a metallated residue



23. (Amended) A composition comprising a compound according to [any one of Claims 1 to 15]Claim 1, together with a pharmaceutically acceptable carrier.

24. (Amended) A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to [any one of Claims 1 to 15]Claim 1 to a mammal in need of such treatment.

25. (Amended) A method according to claim 24, in which the mammal is a human.

28. (New) A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to claim 7 to a mammal in need of such treatment.

29. (New) A method according to claim 28, in which the mammal is a human.

30. (New) A method of reducing or abolishing the central nervous system activity of an opioid structurally related to morphine, comprising the step of linking said opioid structurally related to morphine via the nitrogen, at position 17 thereof, to a spacer group, which in turn is linked to a charged group.